Cohort Study

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Surgical resection for hepatocellular carcinoma: a single-centre's one decade of experience

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Background and aims: Liver cancer is the third leading cause of global cancer deaths, and hepatocellular carcinoma is its most common type. Liver resection is one of the treatment options for hepatocellular carcinoma (HCC). This study aims to explore our hospital's more than a decade of experience in liver resection for HCC patients.

Methods: This is a retrospective cohort study on HCC patients undergoing resection from 2010 to 2021 in a tertiary-level hospital in Jakarta, Indonesia. Mortality rates were explored as the primary outcome of this study. Statistical analysis was done on possible predictive factors using Pearson's χ^2. Survival analysis was done using the Log-Rank test and Cox Regression.

Results: Ninety-one patients were included in this study. The authors found that the postoperative mortality rates were 8.8% (in hospital), 11.5% (30 days), and 24.1% (90 days). Excluding postoperative mortalities, the long-term mortality rates were 44.4% (first year), 58.7% (3 years), and 69.7% (5 years). Cumulatively, the mortality rates were 46.4% (1 year), 68.9% (3 years), 77.8% (5 years), and 67.0% (all time). Significant predictive factors for cumulative 1-year mortality include large tumour diameter [odds ratio (OR) 14.06; 95% CI: 2.59–76.35; comparing <3 cm and >10 cm tumours; $P < 0.01$], positive resection margin (OR 2.86; 1.17–77.0; $P = 0.02$), and tumour differentiation ($P = 0.01$). Multivariate analysis found hazard ratios of 6.35 (2.13–18.93; $P < 0.01$) and 1.81 (1.04–3.14; $P = 0.04$) for tumour diameter and resection margin, respectively.

Conclusion: The mortality rate of HCC patients undergoing resection is still very high. Significant predictive factors for mortality found in this study benefit from earlier diagnosis and treatment; thus, highlighting the importance of HCC surveillance programs.

Keywords: carcinoma, hepatectomy, hepatocellular, liver neoplasms, mortality, prognostic

Introduction

Liver malignancy is the third most common cause of cancer mortality globally, with 830 180 deaths in 2020[1]. In 2020, Indonesia accounted for 20 920 deaths of liver cancer patients[2]. Most (75-85%, globally) primary liver cancer cases are due to hepatocellular carcinoma (HCC)[3]. The HCC is also prominent in Indonesia; an Indonesian tertiary-level national referral hospital reported 158 HCC cases diagnosed from 2015 to 2017, with a 94.4% 3-year mortality rate[4].

Liver resection is one of the HCC treatment modalities, along with liver transplant, radiofrequency ablation (RFA), transarterial chemoembolization (TACE), hepatic arterial infusion chemotherapy (HAIC), and systemic therapy[5]. Liver resection is the first-line treatment option for patients with adequate liver function (Child-Pugh class A or B) and no extrahepatic spread[5].

HIGHLIGHTS

- Liver resection is one of the treatment options for hepatocellular carcinoma. It is the first-line treatment option for patients with adequate liver function and no extrahepatic spread. Patients are also based on Barcelona Clinic Liver Center classifications A and B.
- This article explores hepatocellular carcinoma patients undergoing liver resection from 2010 to 2021 in a tertiary-level hospital in Jakarta, Indonesia. The total population is included, with a total of 91 cases.
- Most patients are middle-aged males with chronic viral hepatitis. More than three out of four patients are assigned Child-Pugh A.
- A total of 201 liver segments are resected. Most of the procedures were done in the right lobe of the liver. The 5-year mortality rate of liver resection in hepatocellular carcinoma is 77.8%, with a quarter of those patients dying in the first 90 days. The mortality increased by 20% in the first and third years.
- Significant prognostic factors include tumour diameter, positive resection margins, and differentiation. Patients with more than 10 cm tumours are ten times more likely to die in the first 90 days and fourteen times more likely to die in the first year.

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article

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Patients undergoing liver resection also have a better (36%) three-year mortality rate than all treatments (94.4%)[4]. However, only 30% of HCC patients are eligible for resection; in addition to adequate liver function and no extrahepatic spread, the resection must also preserve 30–40% postoperative remnant liver volume[6–9]. Due to these strict prerequisites, liver resection patients are a distinct subset from all HCC patients globally.

There has been limited evidence of liver resection for HCC in Indonesia. Only two studies were found; one is an abstract-only study with limited scope, and the other only analyzes results from a 1-year period[10]. Therefore, this study aimed to present the liver resection experience for HCC patients in Indonesia, with mortality rates being the primary objective. In addition, this study evaluated the predictive factors related to the mortality rate for resection patients in our centre.

Methods

Study design

This is a retrospective cohort study on patients undergoing liver resection due to HCC from 2010 to 2021 in a tertiary-level hospital in Jakarta, Indonesia. We analyzed HCC cases to explore patients' characteristics and possible predisposing factors of mortality after surgery. This study has been reported in line with the STROCSS criteria[11].

Study population

The inclusion criteria for this study were patients undergoing liver resection in our centre from 2010 to 2021 due to a confirmed diagnosis of HCC. Patients undergoing liver resection in other hospitals were excluded, even though diagnosis or further care was done in our centre. In addition, patients with other malignancies or undergoing other treatment methods were excluded.

This study used a total population sampling. We included 91 cases, from the first liver resection in 2010 to the most recent in 2021. Clinical, laboratory, and radiological data were collected from the medical records. Follow-up was done once in January 2022 to confirm mortality status by contacting patients or family members.

Treatment of hepatocellular carcinoma patients in our centre

HCC patients are managed by a multidisciplinary team (MDT) consisting of hepatologists, radiologists, pathologists, radiation oncologists, surgeons, and other specialists related to the patient's condition. Baseline data -including age, sex, and important clinical data (presence of ascites, oedema, jaundice, etc.), were collected during the initial outpatient visit. Laboratory evaluation was done within one month of the operation, including prothrombin time, bilirubin, albumin, alpha-fetoprotein, and liver enzyme levels. The Child-Pugh (CP) score was then calculated using clinical (presence of encephalopathy or ascites) and laboratory (prothrombin time, albumin, and bilirubin levels) data[12]. The patient's liver function is classified from best to worst liver function according to the CP classification A to C[12]. Preoperative diagnosis was confirmed by pathology and radiology. The number of tumours and their sizes were also evaluated in preoperative imaging.

A weekly MDT team meeting discussed the treatment options for confirmed HCC patients. Treatment assignment is done in

Table 1

Characteristics of HCC patients assigned to liver resection

Characteristics	Patients (*N* = 91)
Age at operation, median (IQR)	54 (21)
Age at operation, *n* (%)	
< 60	55 (60.4)
> 60	36 (39.6)
Sex, *n* (%)	
Male	68 (74.7)
Female	23 (25.3)
AEtiology, *n* (%)	
NBNC	34 (37.4)
HBV	49 (53.8)
HCV	8 (8.8)
Preoperative Child-Pugh Classification, *n* (%)	
A	78 (85.7)
B	13 (14.3)
Preoperative BCLC Classification, *n* (%)	
A	49 (53.8)
B	42 (46.2)
Preoperative AFP Level	
< 400	57 (62.6)
> 400	34 (37.4)
Preoperative liver enzyme level, median (IQR)	
SGOT	53 (45)
SGPT	47 (41)
Single/multiple (> 1) tumours, *n* (%)	
Single	30 (33.0)
Multiple	61 (67.0)
Largest diameter of tumour, median (IQR)	7 (9)
Largest diameter of tumour, *n* (%)	
< 3 cm	18 (19.8)
3–5 cm	18 (19.8)
> 5–10 cm	23 (25.3)
> 10 cm	32 (35.2)
Method of surgery, *n* (%)	
Laparoscopy	8 (8.8)
Open surgery	83 (91.2)
Number of segment(s) resected, *n* (%)	
1	22 (24.2)
2	37 (40.7)
3	22 (24.2)
4	10 (11.0)
Resection margin, *n* (%)	
Negative margin	55 (60.4)
Positive margin	36 (39.6)
Histopathological presence of cirrhosis, *n* (%)	
Yes	41 (45.1)
No	50 (54.9)
Edmondson's Grading, *n* (%)	
1	9 (9.9)
2	18 (18.8)
3	44 (48.4)
4	20 (22.0)
Tumour differentiation (WHO), *n* (%)	
Well	8 (8.8)
Moderate	39 (42.9)
Moderate to poor	18 (19.8)
Poor	26 (28.6)
Vascular invasion, *n* (%)	
Yes	57 (77.0)
No	17 (23.0)
Data not available	17

Table 1

(*Continued*)

Characteristics	Patients (*N* = 91)
Postoperative length of stay, median (IQR)	14 (14)
Postoperative length of stay, *n* (%)	
< 7 days	18 (19.8)
8–14 days	37 (40.7)
> 14 days	36 (39.6)

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Center; HBV, Hepatitis B Virus; HCC, hepatocellular carcinoma; HCV, Hepatitis C Virus; IQR, interquartile range; NBNC, Non-B and Non-C; SGOT, Serum Glutamic Oxaloacetic Transaminase Oxaloacetic Transaminase; SGPT, Serum Glutamic Pyruvic Transaminase Pyruvic Transaminase.

consideration of the Barcelona Clinic Liver Center (BCLC) staging system, patient preference, and other clinical or socioeconomic considerations[13,14]. BCLC staging system stated that resection is considered for patients at very early (BCLC 0) or early (BCLC A) HCC stages; this includes CP class A patients with a single tumour or less than three small (< 3 cm) tumours[13,14]. However, in some cases, clinical and socioeconomic considerations take precedence. One important socioeconomic consideration is that our national health insurance may not cover other treatment options (such as chemotherapy). Therefore, patients with BCLC B staging may be assigned to liver resection in our centre; if the remnant liver is adequate, a free resection margin is possible, and both the MDT and patients have agreed to the treatment.

Being a national referral hospital with a long waiting list for surgery, HCC patients may have a delay of 3–9 months from assignment to the actual surgery. Patients assigned to surgical resection underwent either laparoscopic or open surgery. One to four segments of the liver were removed. Tissue samples were taken for further pathologic examination, including the presence of cirrhosis and cancer tissue in a 1 cm area from the surgical margin. Histological staging using Edmondson-Steiner grade and assessment of tumour differentiation was also done postoperatively.

Study variables

The primary outcome of this study is the mortality rates. We confirmed each patient's mortality status by evaluating the medical records and contacting patients and family members in January 2022. Mortality dates are also collected for patients who did not survive until 1 January 2022. We calculated the survival duration by subtracting the mortality and resection dates. Survival time was evaluated from the first liver resection (for patients who undergo multiple procedures). Then, we use the survival duration to find the postoperative mortality (in hospital, 30 days, and 90 days), long-term mortality (1 year, 3 years, and 5 years), and cumulative mortality rates. The long-term mortality rates excluded the postoperative mortalities; the cumulative mortality rates included them.

The secondary outcomes are factors predicting mortality after resection. Demographic characteristics (age > 60 years and sex)[14], preoperative, operative, and postoperative findings were independent variables. Preoperative variables include the aetiology of HCC (viral hepatitis B, hepatitis C, or non-hepatitis B or C); alpha-fetoprotein (AFP) level (> 400); CP Class (A or B); and BCLC Classifications (A or B); as well as the number (single or multiple/more than one tumour); and diameter of the tumour (< 3, 3–5, > 5–10, or > 10 cm[5,7,9,15]. A subgroup analysis on the Child-Pugh scores excluding patients without cirrhosis was also done. The operative variables include the number of resected liver segments and the method of surgery (open surgery or laparoscopy). The postoperative variables are mostly histopathologic findings on samples taken during surgery. The findings include surgical margins, the presence of cirrhosis, vascular invasions, and tumour grading. A free surgical margin is defined as no malignant cell found within 1 cm of the incision[16]. Tumour grading was done according to the Edmondson-Steiner and the WHO classifications[17–20].

Statistical analysis

Statistical analysis was done using the IBM SPSS version 24. Patient characteristics are presented using the median and interquartile ranges for continuous data and percentages for categorical data. Bivariate analysis used Pearson's χ^2, comparing the independent variables with the 90-day, 1-year, cumulative 1-year, and all-time mortality. Survival analysis was done using the Log-Rank test (bivariate). The censor date is 1 January 2022. Statistically significant results from the Log-Rank test will be tested for multicollinearity. Variables that are statistically significant and free from multicollinearity were further analyzed using Cox Regression, and a hazard ratio with a 95% cCI was reported.

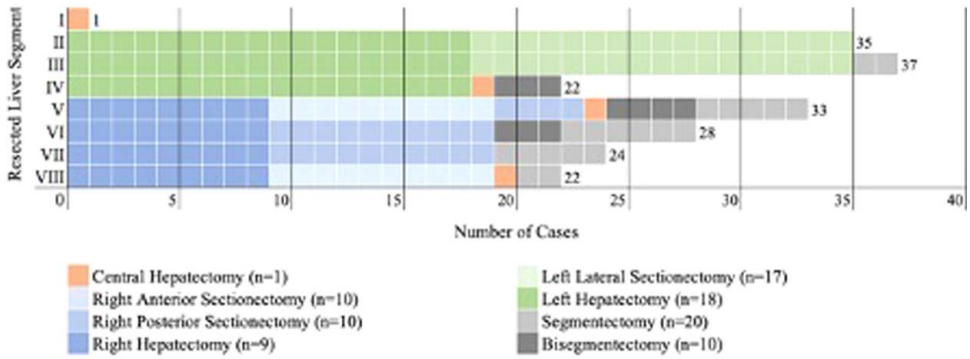

Figure 1. Liver resection procedures done and liver segments resected from 2010 to 2021.

Ethical clearance

The ethics committee of our centre approved this study by giving an ethical clearance with protocol number 19-11-1313. Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Results

Patient's characteristics

Most patients were middle-aged (median age: 54) males (74.7%). The aetiology of HCC is primarily chronic viral hepatitis infection (62.6%), of which 53.8% of the total cases were caused by Hepatitis B. (Table 1). As the CP classification shows, most resection patients have good liver function; 85.7% of HCC patients are CP Class A. The median diameter of the tumours before resection is 7 cm, and most patients (67.0%) have multiple tumours. We estimated that 70% of our resections are anatomical, with the rest being non-anatomical. Almost a fourth of post-resection patients have traces of malignant tissue within 1 cm of the surgical margin. However, all resections done in 2021 had negative surgical margins. The median histopathological classification is grade 3 (Edmondson's) with moderate differentiation. Some data are missing from vascular invasion results, especially those before 2013.

From 2010 to 2021, 91 liver resection procedures were done. From those procedures, a total of 201 liver segments were resected. Most (54 out of 95) procedures were done on the liver's right lobe (segments V–VIII). The left lobe is removed partially or completely in 40 cases. Central hepatectomy is the rarest procedure, with only one procedure done. Segment III is the most often removed segment, with 37 removals, followed by segment II, with 35 cases. The complete recap of all procedures done can be seen in Fig. 1.

Mortality rate

We found that eight resection patients died during their stay in the hospital. The first five mortalities happened during the earlier half of the decade; the cause of death was not recorded. During the latter half, there were three mortalities: one in 2017 and the other two during the COVID-19 pandemic. All three deaths are caused by respiratory failure secondary to postoperative pneumonia. A quarter of post-resection patients died in the first three months post-resection (Table 2). The cumulative mortality rate subsequently increased by 20% in the first and third years. Only 10 (out of 45) patients survived five years after the liver resection.

Factors contributing to mortality

Three parameters show statistically significant 1-year and all-time mortality results: largest tumour diameter, resection margin, and tumour differentiation (Table 3). Patients with tumours sized > 10 cm are ten times more likely to die in the first 90 days [odds ratio (OR) 10.89; 95% CI: 1.27–93.07, $P = 0.01$] and fourteen times more likely in the cumulative first year (OR 14.06; 95% CI: 2.59–76.35, $P < 0.01$) than patients with less than 3 cm tumour. This finding is not found in the first-year mortality if the first 90 days were removed. We also found that the number of segment resected are only statistically significant in the first 90 days.

Positive resection margin is statistically insignificant in the first 90 days; however, it predisposes post-resection mortality in the 1-year subgroup (OR 3.79; 95% CI: 1.23–11.7, $P = 0.02$), cumulative 1 year (OR 2.86; 95% CI 1.17–77.0, $P = 0.02$) and all time (OR 7.17; 95% CI: 2.23–23.03, $P < 0.01$). The tumour differentiation also shows consistent results, with the mortality rate increasing parallel to the histological grading (well to poor).

Survival analysis

Survival analysis (Log-Rank) using the survival duration in months found four statistically significant variables as seen in Table 4: Largest tumour diameter ($P < 0.01$), resection margin ($P < 0.01$), Edmondson grading ($P = 0.04$), and tumour differentiation ($P < 0.01$). However, the Kaplan–Meier survival curve for Edmondson's grading found intersected lines (thus breaking the rule of proportional hazards), resulting in the removal of said variable from Cox Regression. Other variables such as age ($P = 0.61$), assigned sex ($P = 0.24$), aetiology ($P = 0.30$), CP classification ($P = 0.18$), BCLC classification ($P = 0.38$), AFP levels ($P = 0.94$), number of tumours($P = 0.44$), method of surgery ($P = 0.52$), segments resected ($P = 0.66$), cirrhosis ($P = 0.34$), vascular invasion ($P = 0.12$), and length of stay ($P = 0.16$) do not yield significant results and thus are also omitted from Cox Regression.

There is no sign of multicollinearity between all three variables submitted to the multivariate analysis (all variance inflation factor (VIF) < 5). The Omnibus test reveals that the model is a good fit with an overall significance of $P < 0.01$. Tumour size of greater than 10 cm yields the highest mortality risk increase (compared to the reference) with a 6.35 hazard ratio (95% CI: 2.13–18.93, $P < 0.01$). The hazard ratio decreases stepwise for patients with 5–10 cm tumours (hazard ratio 3.67 95% CI: 1.19–11.34, $P = 0.02$) and 3-5 cm tumours (hazard ratio 2.62 95% CI: 0.28–8.32, $P = 0.10$). Another statistically significant result is a positive resection margin with a 1.81 times risk increase (95% CI: 1.04–3.14, $P = 0.04$) compared to those with a negative margin at any given time point. The tumour differentiation is statistically insignificant.

Table 2

The mortality rate of hepatocellular patients post-resection

	Postoperative			Long term[a]			Cumulative			
	In hospital	30 days	90 days	1 year	3 years	5 years	1 year	3 years	5 years	All time
Cases (*n*)	91	78	87	64	46	33	84	61	45	91
Mortality (*n*)	8	9	21	19	27	23	39	42	35	61
Mortality rate (%)	8.8	11.5	24.1	44.4	58.7	69.7	46.4	68.9	77.8	67.0

[a]Excluding mortality which occur in the first 90 days.

Table 3

Factors contributing to 90-day, 1-year, cumulative 1-year, and all-time mortality post-resection

	90-day mortality ($N = 87$)		1-year mortality[a] ($N = 64$)		Cumulative 1-year mortality ($N = 79$)		All-time mortality ($N = 91$)	
Factor	**Mortality, *n* (%)**	***p***	**Mortality, *n* (%)**	***p***	**Mortality, *n* (%)**	***p***	**Mortality, *n* (%)**	***p***
Age		0.778		0.746		0.761		0.692
< 60 years old	12 (23.1)		11 (28.2)		23 (45.1)		36 (65.5)	
> 60 years old	9 (25.7)		8 (32.0)		16 (48.5)		25 (69.4)	
Sex		0.258		0.918		0.528		0.417
Male	14 (21.2)		15 (30.0)		28 (44.4)		44 (64.7)	
Female	7 (33.3)		4 (28.6)		11 (52.4)		17 (73.9)	
AEtiology		0.661		0.726		0.864		0.159
NBNC	6 (18.8)		8 (33.3)		14 (46.7)		20 (58.8)	
HBV	13 (27.7)		10 (29.4)		22 (47.8)		37 (75.5)	
HCV	2 (25.0)		1 (16.7)		3 (37.5)		4 (50.0)	
Child-Pugh Classification		0.191		0.179		0.073		0.856
A	16 (21.6)		15 (26.8)		30 (42.3)		52 (66.7)	
B	5 (38.5)		4 (50.0)		9 (69.2)		9 (69.2)	
Child-Pugh Classification[b]				1.000		0.957		0.271
A	8 (22.9)		9 (33.3)		17 (48.6)		28 (75.6)	
B	1 (25)		1 (33.3)		2 (50.0)		2 (50.0)	
BCLC Classification		0.151		0.863		0.531		0.203
A	8 (17.8)		11 (30.6)		19 (43.2)		30 (61.2)	
B	13 (31.0)		8 (28.6)		20 (50.0)		31 (73.8)	
Preoperative AFP levels		0.593		0.525		0.886		0.577
< 400	12 (22.2)		13 (32.5)		24 (47.1)		37 (64.9)	
> 400	9 (27.3)		6 (25.0)		15 (45.5)		24 (70.6%)	
Single/multiple tumours		0.139		0.922		0.472		0.140
Single	4 (14.3)		7 (30.4)		11 (40.7)		17 (56.7)	
Multiple (> 1)	17 (28.8)		12 (29.3)		28 (49.1)		44 (72.1)	
Largest diameter of tumour		**0.010***		0.172		**0.002***		**0.000***
< 3 cm	**1 (0.67)**		3 (21.4)		**2 (15.4)**		**4 (22.2)**	
3–5 cm	**2 (11.1)**		3 (20.0)		**6 (33.3)**		**11 (61.1)**	
> 5–10 cm	**4 (18.2)**		4 (23.5)		**8 (38.1)**		**18 (78.3)**	
> 10 cm	**14 (43.8)**		9 (50.0)		**23 (71.9)**		**28 (87.5)**	
Surgery method		0.952		0.463		0.594		0.283
Laparoscopy	2 (25.0)		1 (16.7)		3 (37.5)		4 (50.0)	
Open surgery	19 (24.1)		18 (31.0)		36 (47.4)		57 (68.7)	
Segments resected		**0.034**[b]		0.984		0.564		0.802
1	**4 (20.0)**		5 (31.3)		9 (45.0)		13 (59.1)	
2	**5 (13.9)**		9 (31.0)		14 (41.2)		25 (67.6)	
3	**10 (47.6)**		3 (27.3)		12 (60.0)		16 (72.7)	
4	**2 (20.0)**		2 (25.0)		4 (40.0)		7 (70.0)	
Surgical margin		0.505		**0.017**[b]		**0.019**[b]		**0.000***
Negative margin	11 (21.6)		**7 (18.4)**		**17 (35.4)**		**29 (52.7)**	
Positive margin	10 (27.8)		**12 (46.2)**		**22 (61.1)**		**32 (88.9)**	
Presence of cirrhosis		0.835		0.549		0.695		0.259
No	12 (25.0)		9 (26.5)		20 (44.4)		31 (62.0)	
Yes	9 (23.1)		10 (33.3)		19 (48.7)		30 (73.2)	
Edmondson's Grading		0.150		0.397		0.096		**0.008***
1	0		0		0		**2 (22.2)**	
2	2 (11.8)		4 (26.7)		6 (35.3)		**10 (55.6)**	
3	14 (32.6)		9 (31.0)		23 (53.5)		**34 (77.3)**	
4	5 (25.0)		6 (40.0)		10 (52.6)		**15 (75.0)**	
Tumour differention		**0.002***		0.451		**0.013***		**0.000***
Well	**0**		0		**0**		**2 (25.0)**	
Moderate	**4 (10.8)**		10 (29.4)		**14 (38.9)**		**21 (53.8)**	
Moderate to poor	**4 (22.2)**		6 (37.5)		**7 (41.2)**		**13 (72.2)**	
Poor	**13 (50.0)**		3 (33.3)		**18 (69.2)**		**25 (96.2)**	
Vascular invasion		0.483		0.349		0.106		0.108
No	3 (20.0)		1 (14.3)		4 (28.6)		8 (47.1)	
Yes	16 (29.1)		13 (31.7)		25 (47.2)		39 (68.4)	
Length of stay		0.172		0.482		0.164		0.209
< 7 days	4 (25.0)		2 (18.2)		5 (35.7)		11 (61.1)	
8–14 days	5 (14.3)		8 (27.6)		13 (38.2)		22 (59.5)	
> 14 days	12 (33.3)		9 (37.5)		21 (58.3)		28 (77.8)	

Bold values are statistically significant.

AFP, alpha-fetoprotein; BCLC, Barcelona Clinic Liver Center; NBNC, Non-B and Non-C; HBV, Hepatitis B Virus; HCV, Hepatitis C Virus.

[a]Excluding mortality which occur in the first 90 days.

[b]Excluding non-cirrhotic cases.

*Statistically significant ($P < 0.05$).

Table 4

Cox regression of hepatocellular patients post-resection

	Bivariate analysis (Log-Rank)		Multivariate analysis (cox regression)[x]	
Parameters	**χ^2 (df)**	***P***	**Hazard ratio (95% CI)**	***P***
Largest diameter of tumour	21.081 (3)	0.000*		
< 3 (ref.)			1.00	—
3–5 cm			2.62 (0.28–8.32)	0.102
5–10 cm			3.67 (1.19–11.34)	0.024*
> 10 cm			6.35 (2.13–18.93)	0.001*
Resection margin	10.565 (1)	0.001*		
Negative margin (ref.)			1.00	—
Positive margin			1.81 (1.04–3.14)	0.035*
Tumour differention	16.301 (3)	0.001*		
Well (ref.)			1.00	—
Moderate			2.28 (0.52–9.95)	0.271
Moderate to poor			4.34 (0.96–19.61)	0.056
Poor			3.97 (0.90–17.49)	0.069

*values are statistically significant.
ref. reference.

Discussion

In this cohort study, we found that most HCC patients undergoing resection are middle-aged males with chronic Hepatitis B. Patients undergoing liver resection have better clinical parameters (Child-Pugh class) than those undergoing all treatment modalities[4]. This finding is reflected in the mortality rate; patients undergoing all treatment modalities have an overall worse mortality rate[4]. However, mortality rates found in this paper are still high, worse than those found in other Asian countries (46–69.5% 5-year mortality rate)[21]. This difference in mortality rate may be caused by a larger portion of cases in this paper having large (> 5 cm) or multiple tumours, possibly due to the long waiting time[22].

We found that the largest diameter of the tumour, number of segments resected, and tumour differentiation are statistically significant predictive factors for postoperative (90 days) mortality. In addition, the largest diameter of the tumour, positive resection margin, histopathological grading (Edmondson's), and tumour differentiation are statistically significant independent predictive factors for cumulative 1-year and all-time mortality. Interestingly, only the surgical margins are statistically significant in our 1-year analysis if mortalities that happened during the first 90 days are removed. This shows the huge impact the first 90 days have on overall survival.

Predictive factors for mortality in HCC cases are highly contested in previous studies. For example, five studies agreed with our findings that the largest diameter of tumours is an important predictive factor[22–26]. However, five other studies found it not to be statistically significant[27–31]. This large disparity in findings is possibly due to differences in classification, surgical considerations, protocols, and demographic characteristics. Therefore, future studies or reviews may need to take these differences into account.

Based on the HR, tumour size is this paper's most important predictor of mortality. Our findings are similar to Wu *et al.*[32]'s study in 2018, which shows that tumour size is an independent predictor of survival. Larger tumours require more liver segments to be removed, which is a significant predictor of postoperative mortality in this and other studies[33]. Tumour size is also related to tumour differentiation, with extensive or faster-growing tumours having poorer differentiation[34]. However, our analysis found no proof of multicollinearity between tumour size and differentiation (VIF = 1). Tumour differentiation was a significant prognostic factor in our univariate analysis. This result is similar to another study, favoring HCC cases with better tumour differentiation[35].

Positive surgical margin is also an important predictive factor for mortality (according to the survival analysis). In contrast to our postoperative analysis, a statistically significant result is also found in our long-term and cumulative bivariate analysis. This phenomenon may be due to positive surgical margins having a higher risk of tumour recurrence after 1 year[36]. Although a wider resection margin than what is described in this study (> 1 cm) may lead to better long-term overall survival[16,37], ensuring a negative 1 cm surgical margin is not always possible because of anatomical and functional limitations. It should be noted that other studies might use a 1mm or no-ink margin. Blind enlargement of the surgical margin is also not recommended because it could harm normal liver parenchyma[38]. Our centre has improved by implementing intraoperative ultrasonography in 2020; we achieved a 100% negative surgical margin rate in 2021.

Significant predictive factors for mortality found in this study could benefit from earlier diagnosis and treatment; especially given that tumour volume doubling time is 3–4 months, and even more aggressive among Asians due to the higher prevalence of hepatitis B[32]. A good surveillance program for at-risk populations may lead to an improvement in survival by finding HCC patients when they have smaller tumours with better differentiation, both of which are important survival factors in our study and other studies on liver resection[7–9,39,40]. HCC patients found at an earlier stage are also eligible for other curative treatment modalities with better survival[41].

This study is the first long-term evaluation of liver resection for HCC in Indonesia. The main limitation of this study is inadequate documentation of subsequent follow-ups post-surgery. As a national referral hospital, some patients are referred from other cities. After resection, the patients may receive further care locally or be unable to travel for subsequent follow-ups. Therefore, this study did not consider adjunctive treatments, clinical conditions on time points post-resection, recurrence, metastasis, and the cause of death. Another important limitation is that some data -including surgical complications, post-surgical complications, and in-hospital deaths, are not properly recorded because it is older than 5 years (Indonesia's standard active medical record retention period).

Our centre plans to create a registry of HCC patients undergoing resection to overcome this issue. An HCC registry could also be helpful to evaluate and monitor previously insufficiently documented variables, such as intrahepatic metastasis, recurrence, portal vein thrombosis, and invasions to nearby structures. Further studies should use standardized admission, surgical, and discharge forms emphasizing textbook liver outcomes.

Conclusion

One-decade liver resection mortality rate for HCC patients in an Indonesian tertiary-level hospital is high. We found that the largest tumour diameter, positive resection margin, and tumour

differentiation are statistically significant independent predictors for mortality according to bivariate and survival analyses. Most of those prognostic factors benefit from earlier diagnosis and treatment.

Ethical approval

The ethics committee of The Faculty of Medicine, University of Indonesia, approved this study by giving an ethical clearance with protocol number 19-11-1313.

Consent

Written informed consent was obtained from the patients for publication and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

R.A.S., Y.M., A.S.P., and W.S.J. contributed to the development of the study concept and design. Acquisition of data is done by R.A.S., Y.M., N.K.P.S., N.R., F.I., L.S., V.M.G.M., and A.N.L.L. Analysis and interpretation of data, including statistical analysis, are contributed by R.A.S., Y.M., N.K.P.S., V.M.G.M., and A.N.L.L. R.A.S., Y.M., N.K.P.S., F.I., and L.S. drafted the manuscript. The article was then critically revised by A.S.P., W.S.J., N.R., and T.J.M.L. Funding for this research is secured by R.A.S. T.J.M.L. acted as the study supervisor. All authors approved the final submitted version.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

Presentation and registration

The study is registered retrospectively in clinicaltrials.gov (ID: NCT06013657). Data are presented as a poster in the 9th Biennial Congress of the Asian-Pacific Hepato-Pancreato-Biliary Association in Bengaluru, India.

Guarantor

All authors accept the full responsibility for the work, had access to the data, and agreed to publish.

Provenance and peer review

Not commisioned, externally peer reviewed.

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